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[Intervention Protocol]

Antidepressants, benzodiazepines and azapirones for panic disorder in adults: a network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. To compare individual active drugs (antidepressants, benzodiazepines and azapirones) and placebo in terms of efficacy and acceptability in the acute treatment of panic disorder, with or without agoraphobia.

2. To rank treatments for panic disorder (antidepressants, benzodiazepines, azapirones and placebo) according to their effectiveness and acceptability.

BACKGROUND

Description of the condition

A panic attack is a discrete period of fear or anxiety that has a rapid onset, reaches a peak within 10 minutes and in which at least 4 of 13 characteristic symptoms are experienced. Many of these symptoms involve bodily systems, such as racing heart, chest pain, sweating, shaking, dizziness, flushing, churning stomach, faintness and breathlessness. Further recognised panic attack symptoms involve fearful cognitions, such as the fear of collapse, going mad or dying, and derealisation (APA 1994).

Panic disorder first entered diagnostic classification systems in 1980 with the publication of DSM-III, following observations that patients with panic attacks responded to treatment with the tricyclic antidepressant (TCA) imipramine (Klein 1964). To di-

agnose panic disorder, further conditions must be met relating to the frequency of attacks, the need for some to come on 'out of the blue' rather than in a predictable, externally-triggered situation, and exclusions where attacks are attributable solely to medical causes or panic-inducing substances, notably caffeine. DSM-IV requires additionally that at least one attack has been followed by either: a) persistent concern about having additional attacks, b) worry about the implications of the attack or its consequences, or c) a significant change in behaviour related to the attacks (APA 1994). The core features of panic attacks remained unchanged in the DSM-5 (APA 2013), but in DSM-5 panic disorder and agoraphobia are no longer linked and are now coded in two diagnoses (APA 2013a).

Panic disorder is common in the general population with a lifetime prevalence of 1% to 4% (Eaton 1994; Bijl 1998; Kessler 2012). In primary care settings, panic syndromes have been reported to have a prevalence of around 10% (King 2008). Its aetiology is not fully understood and is probably heterogeneous. Biological theories incorporate the faulty triggering of an inbuilt anxiety response, possibly a suffocation alarm. Evidence for this comes from biological challenge tests (lactate and carbon dioxide trigger panic in those with the disorder) and from animal experiments and neuroimaging studies in humans that show activation of fear circuits, such as that involving the periaqueductal grey matter (Gorman 2000).

Agoraphobia is anxiety about being in places or situations from which escape might be difficult or embarrassing, or in which help may not be available in the event of having a panic attack (APA 2013). Agoraphobia can occur with panic disorder (APA 2013). About one quarter of people suffering from panic disorder also have agoraphobia (Kessler 2006). The presence of agoraphobia is associated with increased severity and worse outcome (Kessler 2006). There are several risk factors that predict the development of agoraphobia in people suffering from panic disorder: female gender, more severe dizziness during panic attacks, cognitive factors, dependent personality traits and social anxiety disorder (Starcevic 2009).

Panic disorder, with or without agoraphobia, is highly comorbid with other psychiatric disorders, such as drug dependence, major depression, bipolar I disorder, social phobia, specific phobia, and generalised anxiety disorder (Grant 2006). It is estimated that generalised anxiety disorder co-occurs in 68% of people with panic disorder, whilst major depression has a prevalence of 24% to 88% among people with panic disorder (Starcevic 2009).

Description of the intervention

The treatment of panic disorder includes psychological and pharmacological interventions, often used in combination (Furukawa 2007; Watanabe 2009). Historically, pharmacological interventions for panic disorder have been based on the use of monoamino oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) (Bruce 2003). However, MAOIs and TCAs are burdened by severe adverse effects, such as dietary restrictions (to avoid hypertensive crisis) for MAOIs, and anticholinergic, arrhythmogenic and overall poor tolerability for TCAs (Wade 1999). Benzodiazepines (BDZs), particularly high potency ones, have been used as a safer alternative in panic disorder (Stein 2010), although the long-term outcome may be less good (NICE 2011). Recent international guidelines (BAP 2005; APA 2009; NICE 2011) consider antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), as the first-line treatment for panic disorder, due to their more favourable adverse effect profile over MAOIs and TCAs. A meta-analysis comparing SSRIs and TCAs in panic disorder (Bakker 2002) showed that SSRIs are as effective as TCAs, and are better tolerated, although other studies showed a possible overestimation of the efficacy of SSRIs over older antidepressants in panic disorder (Anderson 2000; Otto 2001). BDZs have higher incidence of dependence and withdrawal reaction when compared to antidepressants (Wade 1999) and may not be effective in treating panic disorder that is comorbid with depression (Ballenger 1998). In spite of these caveats, it appears that BDZs continue to be widely prescribed for the treatment of panic disorder (Bruce 2003). More recently, new research in psychopharmacology has focused on azapirones (Imai 2014), a class of drugs used as anxiolytics, because they seem to be associated with less drowsiness, psychomotor impairment, alcohol potentiation and potential for addiction or abuse than BDZs (Napoliello 1991). Examples include alnespirone, binospirone, buspirone, enilospirone, eptapirone, gepirone, ipsapirone, revospirone, tandospirone and zalospirone, all of which are serotonin 1A (5-HT1A) receptor partial agonists. Other properties include 5-HT2A and α1- and α2-adrenergic receptor antagonism, which differ between individual drugs (Kishi 2013).

How the intervention might work

The main classes with evidence of efficacy in panic disorder are antidepressant drugs that augment the function of the monoamines serotonin and/or noradrenaline. Considering the serotonergic antidepressants (SSRIs such as fluoxetine, paroxetine, sertraline and citalopram) - these drugs promote the transmission of the neurotransmitter serotonin across brain synapses; most notably in the dorsal raphe nucleus (Briley 1993). They prevent reuptake of serotonin into nerve terminals by inhibiting serotonin transporters, thus allowing more to be available for neurotransmission. In panic disorder, imaging studies have revealed reduced expression of the 5H1A receptor (Nash 2008) which has an inhibitory function, so the increased serotonin throughput may in part serve to overcome this deficit of inhibition. Noradrenergic antidepressants can similarly increase transmission of the catecholamine noradrenaline. Some antidepressants such as the serotonin-norepinephrine reuptake inhibitor (SNRI) drugs (e.g. venlafaxine, duloxetine) and TCAs can enhance both serotonin and noradrenaline transmission by inhibiting both transporters. BDZs moderate the gamma-

Aminobutyric acid (GABA) neurotransmitter system, which is the brain's main inhibitory neurotransmitter. They act as agonists at the GABA-A BDZ receptor. This complex contains a chloride channel which can be opened by agonists which ultimately produce anxiolysis and sedation. The BDZ binding site communicates only indirectly with the channel, meaning that BDZs are safer than their predecessors, the barbiturates. It is known through imaging studies that the inhibitory GABA system is deficient in panic disorder (Malizia 1998; Cameron 2007) and thus BDZs' ability to act as agonists at the GABA-A BDZ receptor can counteract this. It is likely that both monoamine-based systems and GABA-based systems converge, allowing both antidepressants and BDZs to have efficacy in panic disorder despite their differing actions on neurotransmitter systems. One possibility is via serotonergic neurons that modulate GABA input to the periaqueductal grey matter.

The exact mechanism of action of azapirones in anxiety disorders has not been established, but they are known to be partial agonists at the serotonin 5-HT1A receptor and potentially as antagonist at dopamine D2 and D3 receptors (Tauscher 2001; Diaz 2011). Although the dopaminergic theory of azapirone action remains unproven, evidence in humans is emerging to confirm that standard therapeutic doses of azapirones such as buspirone can achieve significant D3 receptor occupancy (Payer 2013). Finally, azapirone inhibition of α2-adrenoceptors on serotonergic neurons may also play a role in the anxiolytic effects of buspirone. As these receptors moderate serotonin release, azapirone may be instrumental in increasing overall serotonin availability through this mechanism.

Why it is important to do this review

Antidepressants and BDZs are widely used in clinical practice to treat panic disorder; however, no comprehensive, systematic studies on the matter have been conducted recently. To our knowledge, the last meta-analysis specifically focused on benzodiazepines for panic disorder was published in 1991 (Wilkinson 1991) and the last meta-analysis focusing on antidepressants for this condition was published more than 10 years ago (Bakker 2002). The role of azapirones in panic disorder is still unclear, with only few studies published on the topic (Sheehan 1990; Imai 2014). Standard pair-wise meta-analyses of psychopharmacological interventions in panic disorder are under way within Cochrane (Guaiana 2013a; Guaiana 2013b; Imai 2014; Bighelli 2016). Other reviews have been published on combined psychotherapy and pharmacotherapy in panic disorder (Furukawa 2007; Watanabe 2009). However, given the complexity of the condition and the lack of recent data from systematic reviews on the matter, it is very important to carry out a comprehensive and comparative evaluation of all available treatment options within the framework of a network meta-analysis (NMA). Assessing which treatments, if any, are the most effective and safe, this NMA will help patients, mental health professionals and policy makers identify the best pharmacological treatments for panic disorder, in order to improve clinical practice and patient care.

OBJECTIVES

1. To compare individual active drugs (antidepressants, benzodiazepines and azapirones) and placebo in terms of efficacy and acceptability in the acute treatment of panic disorder, with or without agoraphobia.

2. To rank treatments for panic disorder (antidepressants, benzodiazepines, azapirones and placebo) according to their effectiveness and acceptability.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include double-blind randomised controlled trials (RCTs) comparing against each other, one of the following drugs (see the list below) or placebo, in the acute treatment of panic disorder. Trials in which drugs are used as an augmentation strategy to any other psychotropic drugs will be excluded. For trials which have a cross-over design, we will only consider results from the first randomisation period. Cluster-randomised trials will be included only if intracluster correlation coefficients are reported.

We will exclude:

- relapse prevention trials;
- studies in patients with a diagnosis of panic disorder where the effects of treatments are measured after panic attacks have been induced (for example with CO2 inhalations or lactate infusions);
- studies administering psychosocial therapies targeted at panic disorder concurrently;
- studies comparing psychosocial interventions; and
- quasi-randomised trials.

Types of participants

The fundamental assumption underpinning a network meta-analysis is that of consistency/transitivity (Caldwell 2005; Cipriani 2013). We assume that any patient who meets the inclusion criteria below is, in principle, equally likely to have been randomised to any of the eligible interventions examined in this review, i.e. they are 'jointly randomisable' (Salanti 2012).

Participant characteristics

Patients aged 18 or older, of either sex, with a primary diagnosis of panic disorder, with or without agoraphobia.

Diagnosis

Diagnosis will be according to any of the following criteria: DSM-III-R, DSM-IV or ICD-10. We will not adopt studies using operationalised criteria before DSM-III-R because their conceptualisation of panic disorder is substantively different.

Comorbidities

When the study eligibility focuses on agoraphobia rather than panic disorder, and is operationally diagnosed according to the above-named criteria, and when it can be safely assumed that at least some of the patients are suffering from panic disorder as defined by the above criteria, such a study can still be included. Considering that over 95% of patients with agoraphobia seen clinically suffer from panic disorder as well (Goisman 1995), the effect of their inclusion will be examined in a subgroup analysis. Trials in which all participants have a concurrent primary diagnosis of Axis I or II disorders other than panic disorder or agoraphobia will be excluded if the focus is not the treatment of panic disorder. We will exclude trials in which participants have a serious concomitant medical illness.

Setting

Inpatient, outpatient and primary care.

Subset data

Trials that provide data on a relevant subset of their participants will not be included.

Types of interventions

We will include only studies where medications were used at therapeutic dosage. We define therapeutic doses as doses that are indicated for panic disorder by any of the North American, European or Japanese regulatory agencies. Where such are not available, we will follow the same dose ranges as for major depression (for antidepressants) and generalised anxiety disorder (for benzodiazepines).

Antidepressants

- TCAs and heterocyclics antidepressants: clomipramine, desipramine, dosulepin/dothiepin, doxepin, impiramine, lofepramine, maprotiline, nortriptyline.
- Selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.
- Monoamine-oxidase inhibitors: moclobemide, phenelzine, tranylcypromine.
- Serotonin-noradrenaline reuptake inhibitors: desvenlafaxine, duloxetine, milnacipran, venlafaxine.
- Noradrenergic and specific serotonergic antidepressants: mirtazapine.
- Noradrenergic and dopaminergic reuptake inhibitors: bupropion.
- Noradrenergic reuptake inhibitors: reboxetine.
- Others: agomelatine, trazodone, nefazodone, mianserin, maprotiline, vortioxetine and non-conventional herbal products (e.g. Hypericum)

Benzodiazepines (BDZs)

Alprazolam, bretazenil, bromazepam, chlordiazepoxide, cinolazepam, clonazepam, cloxazolam, clorazepate, deloramzeapam, diazepam, estazolam, etizolam, fludiazepam, flunitrazepam, flurazepam, flutoprazepam, halazepam, ketazolam, loprazolam, lorazepam, lormatezepam, medazepam, nimatazepam, nitrazepam, nodazepam, oxazepam, phenazepam, pinazepam, prazepam, premazepam, quazepam, temazepam, tetrazepam, triazolam and any other drug belonging to the BDZ class.

Azapirones

Alnespirone, binospirone, buspirone, enilospirone, eptapirone, gepirone, ipsapirone, revospirone, tandospirone and zalospirone.

Placebo

Placebo can be active (i.e. mimicking side effects) or inactive (completely inert). We will include studies using active and inactive placebo. This could be a potential source of intransitivity.

If a study has two or more arms at different doses of the same medication within the therapeutic range, we will combine groups to create a single pair-wise comparison, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (chapter 16.5.4) (Higgins 2011).

Types of outcome measures

Studies that meet the above inclusion criteria will be included regardless of whether they report on the following outcomes.

Primary outcomes

1. Response to treatment (i.e. substantial improvement from baseline as defined by the original investigators). We will consider as response the following definitions: "much or very much improved" according to the Clinical Global Impression Change Scale; more than 40% reduction in the Panic Disorder Severity Scale score; or

more than 50% reduction in the Fear Questionnaire Agoraphobia Subscale. When multiple measures are used, preference will be given to the most global measure.
2. Total number of dropouts due to any reason (as a proxy measure of treatment acceptability).

Secondary outcomes

3. Remission (i.e. satisfactory end-state as defined by global judgment of the original investigators). Examples would be "panic free" and "no or minimal symptoms" according to the Clinical Global Impression Severity Scale. When multiple measures are used, preference will be given to the most global measure.
4. Panic symptom scales and global judgment on a continuous scale. Examples include Panic Disorder Severity Scale total score (0 to 28), Clinical Global Impression Severity Scale (1 to 7), and Clinical Global Impression Change Scale (1 to 7).
5. Frequency of panic attacks (as recorded, for example, by a panic diary).
6. Agoraphobia (as measured, for example, by the Fear Questionnaire, Mobility Inventory, or behavioural avoidance test).
When more than one scale is available in the paper, preference will be given in the following order:

- PDSS > Panic and Agoraphobia Scale (PAS) > ASI-R > ASI > ACQ > BSQ > other scales specific for panic disorder;
- CGI-S > CGI-I > GAS > GAF > other global scales;
- FQ-ag > FQ-global > Mobile Inventory for Agoraphobia-Avoidance-Alone (MI-AAL) > MI-Avoidance-Accompanied (MI-AAC) > other scales specific for agoraphobia only; and
- Panic frequency > panic severity > other scales specific for panic attacks only.

Once the scale has been chosen, if both self- and observer-rated assessments are available, preference will be given to the latter. The actual measure entered into the meta-analysis is indicated at the top of the listings in the table 'Characteristics of included studies'.

Timing of outcome assessment

All outcomes are short-term, which we define as acute phase treatment which normally would last two to six months. When studies report more response rates at different time points within two to six months, the time point closest to three months (i.e. 12 weeks) will be given preference.

Hierarchy of outcome measures

When several possible outcome measures are reported for the same outcome, we will use the primary outcome according to the original study.

Search methods for identification of studies

Trials which include at least two of the interventions are eligible for inclusion in the review. We will search for all possible comparisons formed by the interventions of interest, as defined above.

The Cochrane Common Mental Disorders Specialised Register (CCDANCTR)

The Cochrane Common Mental Disorders Group (CCMD) maintains two clinical trials registers at its editorial base in Bristol, UK: a references register and a studies-based register. The CCDANCTR-References Register contains over 37,500 reports of RCTs in depression, anxiety and neurosis. Approximately 60% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual, using a controlled vocabulary. The CCDAN Information Specialist is able to provide further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950-), Embase (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trials registers via the World Health Organization's trials portal (the International Clinical Trials Registry Platform (ICTRP)), pharmaceutical companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.
Details of CCMD generic search strategies (CCDAN's generic search strategies) (used to identify RCTs) can be found on the Group's website.

Electronic searches

1. Cochrane Specialised Register

The CCDANCTR-Studies Register will be searched on condition alone.
Condition = *panic*
Records will be manually screened for drug therapy trials.
The CCDANCTR-References Register will be searched using a more sensitive set of free-text terms to identify additional untagged/uncoded reports of RCTs (Appendix 1).
A further search of the CCDANCTR will be conducted to identify drug therapy trials for 'Anxiety Disorders Not Otherwise Specified' (ADNOS), which may include a subset of participants with panic disorder.
No restrictions on date, language or publication status will be applied to the searches.

2. Biomedical database searches

With the relocation of the Cochrane Common Mental Disorders Group to the University of York in 2016, the CCMDCTR is currently out-of-date, so additional searches will also need to be conducted on the following databases:

1. Cochrane Library (http://www.cochranelibrary.com/) (latest issue);
2. Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (2014 to date);
3. Ovid Embase (2014 to date); and
4. Ovid PsycINFO (2014 to date).

Full search strategies are displayed in Appendix 2.

3. International trial registries

International trial registries will be searched via the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov to identify unpublished or ongoing studies.

Searching other resources

Two review authors will check independently the reference lists of all included studies, non-Cochrane systematic reviews and major textbooks of affective disorders (written in English), for published reports and citations of unpublished research. A citation search will also be conducted via the Web of Science (included studies only) to identify additional works. We will also contact experts in the field.

Data collection and analysis

Selection of studies

At least two review authors will independently screen titles and abstracts for inclusion of all the studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publications and two review authors will independently screen them and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. The two review authors will resolve any disagreement through discussion or, if required, they will consult a third member of the review team. We will identify and exclude duplicate records and we will collate multiple reports that relate to the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form to extract study characteristics and outcome data, which has been piloted on at least one study in the review. Two authors from the review team will extract study characteristics and outcome data from included studies.

From each included study we will extract data on the following study, intervention and population characteristics that may act as effect modifiers.

1. Methods: study design, randomisation (individual or cluster), total duration of study, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, setting, diagnostic criteria, presence or absence of medical and psychiatric comorbidities, presence or absence of elderly participants, percentage of patients with agoraphobia, percentage of patients with baseline depression, inclusion criteria, and exclusion criteria.
3. Interventions: medication dose, medication dose range, use of rescue medication.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. Where possible we will extract data at the arm level, not summary effects.
5. Notes: sponsorship/funding for trial, and notable conflicts of interest of trial authors.

We plan to compile a table of important trial and patient characteristics and visually inspect the similarity of factors we consider likely to modify treatment effect.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person. One review author will transfer data into the Review Manager (RevMan 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

To assess the quality (internal validity) of trials, we will use predefined criteria based on those developed by Cochrane. Inadequate concealment undermines the principle of randomisation, because participants may then be allocated to a treatment according to prognostic variables rather than by pure chance. Therefore, two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author. We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.

6. Selective outcome reporting.

We will judge each potential source of bias as high, low or unclear and provide a supporting quotation from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported anxiety scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Where inadequate details of randomisation and other characteristics of trials are provided, we will contact the authors of the studies in order to obtain further information. Non-concurrence in quality assessment will also be reported.

Measures of treatment effect

Dichotomous data

For binary outcomes we will calculate a standard estimation of the random-effects model risk ratio (RR) and its 95% confidence interval (CI). It has been shown that a random-effects model has a good generalisability (Furukawa 2002) and that RR is more intuitive (Boissel 1999) than odds ratio. Furthermore, odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This may lead to an overestimation of the impression of the effect (Higgins 2011). For all primary outcomes we will calculate the number needed to treat for an additional beneficial or harmful outcome (NNTB or NNTH) and its 95% CI using Visual Rx (www.nntonline.net/), taking account of the event rate in the control group.

Continuous data

(1) Summary statistics

It is likely that different studies have used varied panic rating scales; therefore we will use standardised mean difference (SMD). If all included studies have used the same instrument, we will use mean difference (MD).

(2) Endpoint versus change data

Trials usually report results either using endpoint means and standard deviation (SD) of scales or using change in mean values from baseline of assessment rating scales. We prefer to use scale endpoint data, which typically cannot have negative values and are easier to interpret from a clinical point of view. If endpoint data are unavailable, we will use the change data in separate analyses. In case we use MD, we will pool results based on change data and endpoint data in the same analysis.

Considering that clinical trials for panic disorder are usually small and that data distribution is difficult to assess for studies with small samples, in this review priority will be given to the use and analysis of dichotomous variables both for efficacy and acceptability. Where outcome data or SDs are not recorded, authors will be asked to supply the data. When only the standard error (SE) or t-statistics or P values are reported, SDs will be calculated according to Altman (Altman 1996). In the absence of data from the authors, the mean value of known SDs will be calculated from the group of included studies according to Furukawa and colleagues (Furukawa 2006). We will check that the original SDs are properly distributed, so that the imputed SD represents the average.

Relative treatment rankings

We will estimate the ranking probabilities for all treatments of being at each possible rank. We will also obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks (Salanti 2011). SUCRA can also be re-expressed as a percentage interpreted as the percentage of effectiveness/acceptability of an intervention that would be ranked first without uncertainty.

Unit of analysis issues

Cluster-randomised trials

In cluster-randomised trials groups of individuals rather than individuals are randomised to different interventions. If we identify cluster placebo-controlled randomised trials, we will use the generic inverse variance technique, if such trials have been appropriately analysed taking into account intraclass correlation coefficients to adjust for cluster effects. Where trialists have not adjusted for the effects of clustering, we will attempt to do this by obtaining an intracluster correlation coefficient and then following the guidance given in chapter 16.3.4 of the *Cochrane Handbook* (Higgins 2011).

Cross-over trials

Crossover trials are trials in which all participants receive both the control and intervention treatment but in a different order. The major problem is a carry-over effect from the first phase to the second phase of the study, especially if the condition of interest is unstable (Elbourne 2002). As this is the case with panic disorder, randomised cross-over studies will be included but only data up to the point of first cross-over will be used.

Studies with multiple treatment groups

For the standard, pair-wise meta-analysis, if the arms involve one placebo arm and two or more arms of different classes of antidepressants, we will compare each arm with placebo separately. In this case, a possibility of unit of analysis error can occur, resulting in double counting. In order to avoid that, we will include each pair-wise comparison separately, according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, section 16.5.4 (Higgins 2011). If the variable is dichotomous, we will divide the shared intervention group evenly among the comparisons. If the variable is continuous, only the total number of participants will be divided up, and the means and SDs will be left unchanged.

For the network meta-analysis, multi-arm studies where the same medication at different doses is compared will remain intact with no adjustments to the numerator or denominator of the shared intervention group. We will account for the correlation between the effect sizes from multi-arm studies using the approach suggested in Higgins 1996 and Dias 2013.

Dose-ranging studies

Dose-ranging studies, i.e. where different doses of the same medication are compared to each other, will also be included and the different dose arms will be pooled and considered to be one so long as they are within the standard range (see above).

Dealing with missing data

We will try to contact the study authors for all relevant missing data.

(1) Dichotomous outcomes

Response, or remission on treatment, will be calculated using an intention-to-treat analysis (ITT). We will follow the principle 'once randomised always analysed'. Where participants left the study before the intended endpoint, it will be assumed that they would have experienced the negative outcome. The validity of the above assumption will be tested by sensitivity analysis, applying worst and best case scenarios. When dichotomous outcomes are not reported but the baseline mean and SD on a panic disorder scale are reported, we will calculate the number of responding or remitted participants according to a validated imputation method (Furukawa 2005). The validity of the above approach will be analysed by sensitivity analysis. If necessary, authors of studies will be contacted to obtain data and/or clarification.

(2) Continuous outcomes

Concerning continuous data, the *Cochrane Handbook* recommends avoiding imputation of continuous data and suggests using the data as presented by the original authors. Where ITT data are available they will be preferred to 'per-protocol analysis'. If necessary, authors of studies will be contacted to obtain data and/or clarification.

(3) Skewed or qualitative data

Skewed and qualitative data will be presented descriptively.

Several strategies will be considered for skewed data. If papers report a mean and SD and there is also an absolute minimum possible value for the outcome, we will divide the mean by the SD. If this is less than two then we will conclude that there is some indication of skewness. If it is less than one (that is the SD is bigger than the mean) then there is almost certainly skewness. If papers have not reported the skewness and simply report means, SDs and sample sizes, these numbers will be used. Because there is a possibility that these data may not have been properly analysed, and can also be misleading, analyses will be conducted with and without these studies. If the data have been log-transformed for analysis, and the geometric means are reported, skewness will be reduced. This is the recommended method of analysis of skewed data (Higgins 2011). If papers use non-parametric tests and describe averages using medians, they cannot be formally pooled in the analysis. We will follow the recommendation made in the *Cochrane Handbook* that results of these studies be reported in a table in our review, along with all other papers. This means that the data will not be lost from the review and the results can be considered when drawing conclusions, even if they cannot be formally pooled in the analyses.

(4) Missing statistics

When only P or SE values are reported, we will calculate SDs (Altman 1996). In the absence of supplementary data after requests to the authors, the SDs will be calculated according to a validated imputation method (Furukawa 2006). We will examine the validity of these imputations in the sensitivity analyses.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10 of the *Cochrane Handbook* (Higgins 2011). A funnel plot is usually used to investigate publication bias. However, it has a limited role when there are only few studies of similar size. Secondly, asymmetry of a funnel plot does not always reflect publication bias. Visual inspection of funnel plots will be used to assess publication bias as well as the statistical test for funnel plot asymmetry proposed by Eggers or Rücker (Higgins 2011). We will not use funnel plots for outcomes if there are 10 or fewer studies, or if all studies are of similar size. We will examine small study effects, including publication bias, in the network through network meta-regression (Chaimani 2012).

Assessment of transitivity across treatment comparisons

Transitivity characterises a network of interventions when the distributions of potential effect modifiers (as described above) are balanced across all pair-wise comparisons. Transitivity can be in-

terpreted as the extension of the clinical and methodological heterogeneity across the network of different comparisons, and is necessary to ensure a valid network meta-analysis. We will evaluate transitivity in this review as follows.
(1) We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; for example, whether antidepressants are administered in the same way in studies comparing antidepressants to placebo and in those comparing antidepressants to benzodiazepines.
(2) We will compare the distribution of the potential effect modifiers across the different pair-wise comparisons.

Data synthesis

Methods for direct comparisons (pair-wise meta-analysis)

Random-effects pair-wise meta-analyses will be conducted for every treatment comparison with at least two studies, using Stata 2013 (StataCorp 2013). A random-effects model is considered preferable here since it allows for variation across studies even when there is no evidence of statistical heterogeneity. It gives a more conservative estimate than the fixed-effect model. We note that the random-effects model gives added weight to small studies, which can either increase or decrease the effect size. We will also apply a fixed-effect model, on primary outcomes only, to see whether it markedly changes the effect size.

Methods for network meta-analysis (NMA)

A random-effects NMA, taking into account the correlations induced by multi-arm trials, will be conducted in a Bayesian framework and implemented using WinBUGS 1.4.3 (Winbugs 2012). There are three possible models that could be fitted.

1. A class (lumped) model.
2. An individual treatment (possibly dose-specific) model.
3. A hierarchical model where we include both class and treatments.

We will investigate models depending on the available data. The goodness of fit of the model to the data will be measured by the posterior mean of the residual deviance. This is defined as the difference between the deviance for the fitted model and the deviance for the saturated model, where deviance measures the fit of the model to the data points using the likelihood function. Where necessary we will examine leverage plots to help identify any specific data points (trial arms) that were fitting poorly in each model. A leverage plot displays the leverage (a measure of influence equal to the contribution of each trial arm to $P_{D,}$ the effective number of parameters) versus the signed, square root of the residual deviance (a measure of fit) for each data point. Points with a high leverage are influential, which means that they have a strong influence on the model parameters that generate their fitted values. Convergence will be assessed using two chains and based on the Brooks-Gelman-Rubin diagnostic tool in WinBUGS.

Assessment of statistical heterogeneity

In the standard pair-wise meta-analyses we will allow separate heterogeneity variances to be estimated for each pair-wise comparison (as is the standard approach in Cochrane systematic reviews). In the NMA we will assume an homogeneous between-study variability across studies (Lu 2004).
For the pair-wise meta-analyses we will statistically assess heterogeneity using the I^2 statistic, using the following thresholds to aid interpretation (section 9.5.2, Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

We will also use the Chi^2 test and its P value to determine the direction and magnitude of the treatment effects. A P value of 0.10 will be used as a threshold of statistical significance, since the Chi^2 test may be underpowered to detect statistical heterogeneity should it exist.
For the NMA the statistical assessment of heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter, Tau^2 estimated from the model. For dichotomous outcomes the magnitude of the heterogeneity variance will be compared with the empirical distribution derived by Turner (Turner 2012). Empirical distributions for Tau^2 have been developed recently also for continuous data (Rhodes 2015).
Inconsistency can be considered an additional layer of heterogeneity which can occur in networks of evidence. It can occur when there is a discrepancy between a direct and indirect estimate of treatment effect. As a first step, we will investigate the presence of inconsistency locally, using a 'loop-specific' approach. A loop of evidence is formed by at least three treatments which have been compared in studies forming a closed path in the network (e.g. the triangle A-B-C). We will calculate the difference between indirect and direct estimates in each closed loop and apply a loop-specific z-test. We will report the percentage of inconsistent loops in the network. The loop-specific approach cannot infer about inconsistency across the whole network. We will also use global goodness-of-fit statistics to compare a model assuming consistency with a model that does not. In case of considerable inconsistency we will investigate possible sources of it (e.g. mistakes in data extraction or in data entry).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses are often exploratory in nature and should be interpreted cautiously: firstly, because they often involve multiple analyses leading to false positive results; and secondly, because these analyses lack power and are more likely to result in false negative

results. Therefore, we will perform the following subgroup analysis on the primary outcomes only.

- People suffering from panic disorder without agoraphobia versus people suffering from panic disorder with agoraphobia.

Sensitivity analysis

The following sensitivity analyses have been planned a priori. We will examine if the results change and check for the robustness of the observed findings by:

1. excluding trials with imputed response rate; and
2. studies using as hoc outcome scale versus studies using a validated scale (for responses and remission outcomes only).

Our routine comparisons of random-effects and fixed-effect models, as well as our secondary outcomes of remission rates and continuous severity measures, may be considered additional forms of sensitivity analyses.

'Summary of findings' table

There is no currently agreed format for 'Summary of findings' tables from NMAs. However, in case a format for such a table becomes available during the preparation of this review, we may decide to use it and we will summarise the findings, applying the GRADE approach (Higgins 2011).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CCDANCTR-References Register search

CCDANCTR-Refs Search 1 (panic):

#1. panic or agoraphobi*

#2. (antidepress* or anti-depress* or "anti depress*" or MAOI* or RIMA* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) NEAR (uptake or reuptake or re-uptake or "re uptake")) or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or pharmacotherap* or psychotropic* or "drug therapy")

#3. (agomelatine or alaproclate or amoxapine or amineptine or amitriptylin* or amitriptylinoxide or atomoxetine or befloxatone or benactyzine or binospirone or brofaromine or (buproprion or amfebutamone) or butriptyline or caroxazone or cianopramine or cilobamine or cimoxatone or citalopram or (chlorimipramin* or clomipramin* or chlomipramin* or clomipramine) or clorgyline or clovoxamine or (cx157 or tyrima) or demexiptiline or deprenyl or (desipramine* or pertofrane) or desvenlafaxine or dibenzepin or diclofensine or dimetacrin* or dosulepin or dothiepin or doxepin or duloxetine or desvenlafaxine or dvs-233 or escitalopram or etoperidone or femoxetine or fluotracen or fluoxetine or fluvoxamine or (hyperforin or hypericum or "st john*") or imipramin* or iprindole or iproniazid* or ipsapirone or isocarboxazid* or levomilnacipran or lofepramine* or ("lu aa21004" or vortioxetine) or "lu aa24530" or (ly2216684 or edivoxetine) or maprotiline or melitracen or metapramine or mianserin or milnacipran or minaprine or mirtazapine or moclobemide or nefazodone or nialamide or nitroxazepine or nomifensine or norfenfluramine or nortriptylin* or noxiptilin* or opipramol or oxaflozane or paroxetine or phenelzine or pheniprazine or pipofezine or pirlindole or pivagabine or pizotyline or propizepine or protriptylin* or quinupramine or reboxetine or rolipram or scopolamine or selegiline or sertraline or setiptiline or teciptiline or thozalinone or tianeptin* or toloxatone or tranylcypromin* or trazodone or trimipramine or venlafaxine or viloxazine or vilazodone or viqualine or zalospirone)

#4. (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or "ethyl loflazepate" or "cm 6912" or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or "wy 3498" or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or (zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or "z drugs") or *pam or *lam)

#5. (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone or *piron*)

#6. (#1 and (#2 or #3 or #4 or #5))
CCDANCTR-Refs Search 2 (ADNOS) :
#7. ((anxiety or anxious or ADNOS) and not (agoraphobi* or panic or (social NEAR (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or "post trauma*" or posttrauma*))
#8. (#7 and (#2 or #3 or #4 or #5))

Appendix 2. Other database searches

Biomedical database update searches will be restricted from 2014 to present.

Ovid MEDLINE databases

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
1 (panic or agoraphobi*).mp.
2 exp Antidepressive Agents/
3 exp Neurotransmitter Uptake Inhibitors/
4 exp Monoamine Oxidase Inhibitors/
5 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp.
6 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp.
7 exp Benzodiazepines/
8 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs).mp.
9 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone).mp.
10 (placebo* or dummy or sugar pill).mp.
11 or/2-10
12 randomized controlled trial.pt.
13 randomi#ed.ti,ab,kf.
14 controlled clinical trial.pt.
15 Double-Blind Method/

16 clinical trials as topic.sh.
17 randomly.ab.
18 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,kf.
19 trial.ti,kf.
20 (animals not (humans and animals)).sh.
21 or/12-19
22 21 not 20
23 1 and 11 and 22
24 (NLM or HSR).ro.
25 23 and 24
26 (2014* or 2015* or 2016*).yr,ed.
27 25 and 26
28 remove duplicates from 27

Cochrane Central Register of Controlled Trials (CENTRAL)

Current Issue
#1MeSH descriptor: [Panic] this term only
#2MeSH descriptor: [Panic Disorder] this term only
#3MeSH descriptor: [Agoraphobia] this term only
#4(panic or agoraphobi*)
#5#1 or #2 or #3 or #4
#6MeSH descriptor: [Antidepressive Agents] explode all trees
#7MeSH descriptor: [Neurotransmitter Uptake Inhibitors] explode all trees
#8MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees
#9(antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*)
#10(Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone)
#11MeSH descriptor: [Benzodiazepines] explode all trees
#12(benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs)

#13(azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone)
#14(placebo* or dummy or "sugar pill*")
#15#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16#5 and #15
#17(2014* or 2015* or 2016* or 2017*)
#18#16 and #17

Ovid Embase

1980 to present
1 Panic/
2 Agoraphobia/
3 (panic or agoraphobi*).mp.
4 or/1-3
5 exp antidepressant agent/
6 exp serotonin uptake inhibitor/
7 exp serotonin noradrenalin reuptake inhibitor/
8 exp noradrenalin uptake inhibitor/
9 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or
Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp.
10 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp.
11 exp Benzodiazepine derivative/
12 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs).mp.
13 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone).mp.
14 (placebo* or dummy or sugar pill*).mp.
15 or/5-14
16 major clinical study/
17 Randomized controlled trial/

18 Controlled clinical study/
19 double blind procedure/
20 randomization/
21 (RCT or randomi#ed).ti,ab,kw.
22 ((at random or random*) adj2 (allocat* or assign* or divide* or division or number)).ti,ab,kw.
23 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw.
24 or/16-23
25 ((animal or nonhuman) not (human and (animal or nonhuman))).de.
26 24 not 25
27 4 and 15 and 26
28 elsevier.cr.
29 27 and 28
30 (random* adj sampl* adj7 ("cross section*" or questionnaire*1 or survey* or database*1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
31 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.
32 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
33 (Systematic review not (trial or study)).ti.
34 (review.ab. and review.pt.) not trial.ti.
35 or/30-34
36 29 not 35
37 (2014* or 2015* or 2016*).yr,dd.
38 36 and 37

Ovid PsycINFO

1987 to present
1 Panic Attack/ or Panic/ or Panic Disorder/
2 Agoraphobia/
3 (panic or agoraphobi*).mp.
4 adnos.ti,ab,id.
5 (anxiety disorder* adj2 otherwise specified).ti,ab,id.
6 or/1-5
7 exp Antidepressant Drugs/
8 Neurotransmitter Uptake Inhibitors/ or exp serotonin norepinephrine reuptake inhibitors/ or exp serotonin reuptake inhibitors/
9 exp Monoamine Oxidase Inhibitors/
10 exp Tricyclic Antidepressant Drugs/
11 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp.
12 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp.

13 exp benzodiazepines/
14 (benzodiazepin* or BZD or abecarnil or adinazolam or alprazolam or arfendazam or bentazepam or bretazenil or bromazepam or brotizolam or camazepam or chlordiazepoxide or chlordesmethyldiazepam or cinolazepam or clobazam or clonazepam or clorazepate or chlorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or desoxydemoxepam or devazepide or diazepam or doxefazepam or estazolam or ethyl loflazepate or cm 6912 or cm-6912 or etizolam or fludiazepam or flunitrazepam or flurazepam or dealkylflurazepam or flutoprazepam or fosazepam or gidazepam or girisopam or halazepam or haloxazolam or ketazolam or loflazepate or loprazolam or lorazepam or lormetazepam or meclonazepam or medazepam or metaclazepam or mexazolam or midazolam or nerisopam or nimetazepam or nitrazepam or norchlordiazepoxide or norclobazam or nordazepam or norfludiazepam or norflunitrazepam or oxazepam or wy 3498 or wy-3498 or oxazolam or phenazepam or pinazepam or prazepam or premazepam or propazepam or quazepam or ripazepam or serazepine or sograzepide or talampanel or tarazepide or temazepam or tetrazepam or tofisopam or triazolam or zolazepam or zaleplon or zolpidem or zopiclone or eszopiclone or z-drugs or z drugs).mp.
15 (azapirone or alnespirone or binospirone or buspirone or enilospirone or eptapirone or gepirone or ipsapirone or revospirone or tandospirone or zalospirone).mp.
16 (placebo* or dummy or sugar pill*).mp.
17 or/7-16
18 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,id.
19 trial.ti,id.
20 randomi#ed.ti,ab,id.
21 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).ti,ab,id.
22 (placebo* or dummy or sugar pill*).mp.
23 or/18-22
24 6 and 17 and 23
25 (2014* or 2015* or 2016*).yr,an.
26 24 and 25
27 ((anxiety or ADNOS) not (agoraphobi* or panic or (social adj3 (anxi* or phobi*)) or generalised or generalized or obsessive or compulsive or OCD or PTSD or post-trauma* or post trauma* or posttrauma*)).ti,id,hw.
28 17 and 23 and 27
29 25 and 28
30 26 or 29

CONTRIBUTIONS OF AUTHORS

GG, CB, MK, TAF and AC conceived the review. GG, DC and AC wrote the draft of the protocol, and all authors critically commented on the protocol. HI, AT , AC, IB and AC will select the studies, appraise their quality and extract data.

DECLARATIONS OF INTEREST

TAF has received lecture fees from Eli Lilly, Meiji, Mochida, MSD, Otsuka, Pfizer and Tanabe-Mitsubishi, and consultancy fees from Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha publishers. He has received grant or research support from the Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, the Japan Foundation for Neuroscience and Mental Health, Tanabe-Mitsubishi and Mochida. He is diplomate of the Academy of Cognitive Therapy.

AT has received honoraria for speaking at a meeting sponsored by Eli Lilly and Tanabe-Mitsubishi.

AC was expert witness for Accord Healthcare in a patent issue about quetiapine extended release.

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Internal sources

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Salary for CB, IB

- University of Bristol, UK.

Salary for DC

- University of Toronto, Canada.

Salary and protected time for SJD

- Kyoto University, Japan.

Salary for TAF, HI, AT

- University of Oxford, UK.

Salary for AC

External sources

- No sources of support supplied